Prognostic Significance of Increased Left Ventricular Mass Index to Mortality and Sudden Death in Patients With Stable Coronary Heart Disease (from the Heart and Soul Study)

Mintu P. Turakhia, MDa,d,*, Nelson B. Schiller, MD, FACCa, and Mary A. Whooley, MDa,b,c

Data are limited about the significance of left ventricular (LV) hypertrophy or mass in patients with coronary heart disease (CHD), particularly in the setting of normal ejection fraction (EF). The association of LV mass index with all-cause mortality and sudden death in a cohort with CHD was evaluated. Using transthoracic echocardiography, LV mass normalized to body surface area was measured in 1,016 subjects with stable CHD. Cox proportional hazards models were used to examine the association of LV mass index and LV hypertrophy (LV mass index >95 g/m² in women and >115 in men) with time to death and time to sudden or arrhythmic death. Mean LV mass index was 101 ± 27 g/m² in men and 88 ± 23 in women. During a mean follow-up of 3.55 years, there were 146 deaths and 34 sudden or arrhythmic deaths. Total mortality was higher in subjects with LV hypertrophy (25% vs 11%, p <0.001), as was mortality from sudden or arrhythmic death (6.7% vs 2.2%, p = 0.001). After adjustment for age, gender, cardiovascular risk factors, and medical therapy, LV hypertrophy was associated with both all-cause mortality (hazard ratio 2.0, p <0.001) and sudden or arrhythmic death (hazard ratio 3.1, p = 0.003). Findings were similar in the subgroup with EF ≥55% (mortality hazard ratio 1.8, p = 0.02; sudden and arrhythmic death hazard ratio 3.1, p = 0.02). Analyzed as a continuous variable, every 20-unit increase in LV mass index increased the adjusted hazard of death by 22% (p = 0.001) and adjusted hazard of sudden or arrhythmic death by 40% (p = 0.004). In conclusion, in patients with stable CHD, increased LV mass index was independently associated with all-cause mortality and sudden or arrhythmic death, even in subjects with normal EF. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;102:1131–1135)

Population studies that showed an association between left ventricular (LV) hypertrophy and mortality have been performed in cohorts with a low prevalence of coronary heart disease (CHD).1–5 Data are limited about the significance of LV hypertrophy or mass in patients with CHD, particularly in the setting of normal ejection fraction (EF). To determine whether LV mass independently predicts all-cause mortality and sudden cardiac death (SCD), we performed echocardiography in 1,016 patients with CHD and assessed cardiovascular outcomes during 3.5 years of follow-up.

Methods

The Heart and Soul Study is a prospective cohort study investigating psychosocial factors and health outcomes in patients with coronary artery disease. Details regarding methods and study design have been previously published.6 From September 2000 to December 2002, a total of 1,024 patients were recruited from 2 Veterans Affairs Medical Centers (San Francisco and Palo Alto, California), 1 university-based medical center (University of California, San Francisco), and 9 public health clinics in the Community Health Network in San Francisco. Eligible participants had ≥1 of (1) history of myocardial infarction, (2) angiographic evidence of ≥50% stenosis in ≥1 coronary vessel, (3) evidence of exercise-induced ischemia using treadmill electrocardiogram or stress nuclear perfusion imaging, or (4) history of coronary revascularization. Patients were excluded from the Heart and Soul Study if they were unable to walk 1 block, experienced a myocardial infarction within the previous 6 months, or were planning to move from the local area within 3 years. Of 1,024 study subjects, 1,016 (99%) had complete echocardiographic measurements and were the subjects of this secondary analysis.

Baseline resting 2-dimensional echocardiography with Doppler imaging was performed using a standardized protocol by 1 of 3 identical cardiac ultrasound systems (Siemens Medical, Malvern, Pennsylvania). LV volumes were calculated using the truncated ellipse formula and Simpson’s rule using planimetry of standard parasternal short-axis and apical 2- and 4-chamber views.7 EF was calculated as (end-diastolic volume − end-systolic volume)/(end-diastolic volume). LV mass was derived from wall thickness...
The primary predictor variable, LV mass, was normalized to body surface area to calculate LV mass index, which had a normal distribution. LV mass index was analyzed as a continuous variable. LV hypertrophy was defined as LV mass index >95 g/m² in women and >115 in men using the most recent guidelines. We considered using an older definition based on LV mass index >110 g/m² in women and >134 in men, but these values were set at >2 standard deviations greater than the mean (97th percentile) from 1 population study and may fail to capture risk at lower values of increased LV mass index because of reduced sensitivity.

Differences in baseline characteristics stratified by LV hypertrophy were compared using chi-square test for categorical variables and t test for continuous variables. Cumulative event-free survival was measured using the Kaplan-Meier method, and unadjusted differences were compared using log-rank test. To assess the independent value of LV hypertrophy for predicting death and sudden/arrhythmic death, we performed Cox regression analysis and adjusted for baseline clinical variables selected on the basis of face validity that were associated with LV mass quartiles at p ≤0.10. The Cox model assumption of proportional hazards was found to be valid using log-minus-log curves and Schoenfeld test. Analyses were repeated in the subgroup of patients with normal EF at rest (≥55%). Statistical analyses were performed using STATA, version 9.0 (StataCorp, College Station, Texas). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the report as written.

Results

In the 1,016 participants, mean LV mass indexes were 91 ± 27 g/m² in men and 88 ± 23 g/m² in women. LV hypertrophy was present in 23% of men and 27% of women (p = NS). Mean EF was 62 ± 9.6%, and 82% of patients had a normal EF (≥55%). Subjects with LV hypertrophy were older, more likely to be men, and had a higher prevalence of baseline diabetes mellitus, hypertension, previous myocardial infarction, and heart failure. Subjects with LV hypertrophy were also more likely to be using renin-angiotensin
inhibitors and β blockers. Higher LV mass was also associated with lower EF and higher septal and posterior LV wall thicknesses and LV volumes (Table 1).

During a mean follow-up of 3.55 years, there were 146 deaths (14% of cohort). Mortality information was available for 1,008 of 1,016 subjects (99%). Thirty-four deaths (23%) were caused by sudden or arrhythmic death. Twenty of 34 (59%) sudden or arrhythmic deaths and 95 of 146 (65%) overall deaths were in subjects with normal baseline EF. Total mortality through the end of follow-up was higher in subjects with LV hypertrophy (25% vs 11%, \( p < 0.001 \)). The mortality rate from sudden or arrhythmic death was also higher in subjects with LV hypertrophy (6.7% vs 2.2%, \( p < 0.001 \)).

Kaplan-Meier estimates for the outcomes of death (Figure 1) and sudden/arrhythmic death (Figure 2) showed significantly lower survival for subjects with LV hypertrophy.

After adjustment for age, gender, hypertension, diabetes, heart failure, myocardial infarction, and use of angiotensin blockers, statins, or β blockers, LV hypertrophy was significantly associated with death and sudden/arrhythmic death (Table 2). Analyzed as a continuous variable, every 20-unit increase in LV mass index increased the adjusted hazard of death by 22% (\( p = 0.001 \)) and adjusted hazard of sudden or arrhythmic death by 40% (\( p = 0.004 \)). Findings were similar in the subgroup of patients with normal EF (Table 2). Addition of LV mass index to the full multivariate clinical models significantly improved the clinical model for the outcomes of mortality (likelihood ratio [LR] chi-square 14.0, \( p < 0.001 \)) and sudden or arrhythmic death (LR chi-square 8.8, \( p = 0.003 \)).

We also created a second multivariate model to assess the incremental prognostic value of LV mass index in addition to other significant echocardiographic structural parameters. After adjustment for LV end-systolic volume and EF, LV mass index was significantly associated with death and sudden or arrhythmic death (Table 3). Addition of LV mass index significantly improved the echocardiographic Cox regression models of death and sudden or arrhythmic death (Table 3). For the outcome of death, sensitivity of LV hypertrophy was 42%, specificity was 78%, positive predictive value was 25%, and negative predictive value was 89%. For sudden or arrhythmic death, sensitivity of LV hypertrophy was 49%, specificity was 77%, positive predictive value was 7%, and negative predictive value was 98%.

### Discussion

The principal finding of this observational study was that in patients with stable CHD, LV hypertrophy determined using LV mass index was associated with all-cause mortality and sudden or arrhythmic death independent of other clinical covariates or echocardiographic parameters. These as-

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**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-Cause Mortality</th>
<th></th>
<th>Sudden or Arrhythmic Death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Entire Cohort (n = 1,016)</td>
<td>EF ≥55% (n = 835)</td>
<td>Entire Cohort (n = 1,016)</td>
<td>EF ≥55% (n = 835)</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>2.4 (1.8–3.4)</td>
<td>&lt;0.001</td>
<td>2.0 (1.3–3.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjusted for age and sex</td>
<td>2.3 (1.7–3.2)</td>
<td>&lt;0.001</td>
<td>2.0 (1.2–3.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Adjusted for age, sex, and risk factors*</td>
<td>2.0 (1.4–2.8)</td>
<td>&lt;0.001</td>
<td>1.8 (1.1–2.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for age, sex, risk factors* and medical therapy†</td>
<td>2.0 (1.4–2.9)</td>
<td>&lt;0.001</td>
<td>1.8 (1.1–2.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Risk of LV mass index (/20-g/m² increase), adjusted for age, sex, risk factors*, and medical therapy†</td>
<td>1.22 (1.09–1.37)</td>
<td>0.001</td>
<td>1.20 (1.01–1.4)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio.

* Risk factors: body mass index, smoking, hypertension, diabetes, heart failure, previous myocardial infarction, and previous revascularization.

† Medical therapy: angiotensin blockade, β blockade, and statin therapy.
Table 3

Association of left ventricular (LV) mass index with all-cause mortality and sudden death, adjusted for LV ejection fraction (EF) and end-systolic volume

<table>
<thead>
<tr>
<th>Variable</th>
<th>All-Cause Mortality</th>
<th></th>
<th>Sudden or Arrhythmic Death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p Value</td>
<td>HR (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>End-systolic volume (/20-unit increase)</td>
<td>1.4 (0.96–1.4)</td>
<td>0.14</td>
<td>0.82 (0.55–1.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>EF (/5% decrease)</td>
<td>1.1 (0.94–1.2)</td>
<td>0.28</td>
<td>1.3 (1.05–1.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>LV mass index (/20-unit increase)</td>
<td>1.2 (1.1–1.4)</td>
<td>0.002</td>
<td>1.4 (1.1–1.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>LR chi-square for inclusion of LV mass index into model</td>
<td>9.25</td>
<td>0.002</td>
<td>6.23</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

associations were also present in subjects with normal EF, which represented most of the cohort.

The strongest data showing an association between LV mass index and sudden death were from the Framingham study. However, in this study, the baseline prevalence of CHD and heart failure was low (9.3% combined), unlike in our cohort, in which CHD was a criterion for enrollment (100% prevalence of CHD). In the Framingham study, the adjusted hazard ratio of LV hypertrophy for SCD was 2.16, similar to our own data. The similar risk ratios may be caused by the use of a higher cut-off value to define LV hypertrophy in the Framingham study despite major baseline differences between cohorts.

A notable finding of our study was that LV mass index predicted sudden and arrhythmic deaths that would not have been captured by Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) criteria (EF ≤30%) with reasonable specificity, although sensitivity was low. This may have implications for risk stratification for SCD in patients with CHD and normal EF, particularly because one-half of sudden death occurs in patients with normal LV hypertrophy in the Framingham study despite major baseline differences between cohorts.

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LV hypertrophy may be causally related to arrhythmic mortality through a number of mechanisms. Myocardial fibrosis in hypertrophied regions may facilitate reentrant ventricular arrhythmias, whereas prolonged or heterogeneous ventricular repolarization and reduced coronary flow reserve may increase susceptibility to ventricular fibrillation. Increased LV mass may contribute to diastolic dysfunction, leading to heart failure and associated neurohormonal changes and autonomic dysfunction that may directly predispose to arrhythmias. Finally, rather than being causally related, LV hypertrophy may be a marker for atherosclerosis, endothelial dysfunction, or ventricular remodeling in patients with CHD that represents a phenotype associated with higher arrhythmic risk. However, our findings were significant even after adjustment for previous myocardial infarction, hypertension, and heart failure.

Study limitations: This was an observational study and residual confounding may be present. Because the ability to walk 1 block was an inclusion criterion, subjects with poor functional status or low EF may be underrepresented. Because LV mass and EF were measured at baseline, it is possible that EF could have decreased between the time of the echocardiogram and time of death, although these types of findings represent mediators rather than confounders and would not bias results. Most subjects were enrolled at Veterans Affairs medical centers, which could limit generalizability. LV mass index was calculated by 3 skilled sonographers trained in measurement of LV mass index. If LV mass index measurements were performed by less experienced technicians, increased measurement error and variability may attenuate the observed associations, thus limiting reproducibility. The end point of sudden or arrhythmic death should not be construed as a surrogate for deaths preventable by use of implantable defibrillators because other causes of death, such as pump failure, may also be associated with increased LV mass. Because calculation of LV mass requires measurement of septal and posterior wall thickness and because EF requires measurement of end-systolic and end-diastolic volumes, we limited the number of variables in our echocardiographic model to avoid over-adjustment from highly collinear variables. Finally, although there were relatively few sudden or arrhythmic deaths (34 deaths), no statistical assumptions were violated.

cardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440–1463.


